Movement Disorders
CLINICAL PRACTICE

REVIEW

Clinical Impact of Deep Brain Stimulation on the Autonomic System in Patients with Parkinson's Disease

Gabriele Bellini, MD,[1] Laura A. Best, MD,[1,*] Una Brechany, RGN,[2] Russell Mills, RGN,[2] and Nicola Pavese, MD, PhD[1,3]

ABSTRACT: Background: The role of deep brain stimulation (DBS) in the management of motor symptoms in patients with Parkinson's disease is well defined. However, it is becoming increasingly clear that DBS can either improve or worsen a number of non-motor phenomena.
Objectives: We examined the published literature to better understand the effects on autonomic symptoms following DBS of the subthalamic nucleus and the globus pallidus interna.
Methods: We conducted a PubMed search of studies regarding the effects of DBS on the autonomic system published from January 2001. We searched for the following terms and their combinations: Parkinson's disease, deep brain stimulation, subthalamic nucleus, globus pallidus interna, autonomic dysfunction.
Results: Most studies reported in the literature focus on DBS targeting the subthalamic nucleus, with particular emphasis on favorable outcomes regarding gastrointestinal function and bladder control. However, the emergence or worsening of autonomic symptoms in subgroups of patients has also been documented. More controversial is the effect of stimulation on the cardiovascular, pulmonary, and thermo-regulatory systems as well as sexual functioning. Data regarding the influence of DBS on the autonomic system when the target is the globus pallidus interna is less forthcoming, with target selection varying according to centre and clinical indication.
Conclusions: DBS appears to affect the autonomic nervous system, with varying degrees of influence, which may or may not be clinically beneficial for the patient. A better understanding of these effects could help personalize stimulation for individual patients with autonomic disorders and/or avoid autonomic symptoms in susceptible patients.

Deep brain stimulation (DBS) is a surgical technique in which small electrodes are positioned within specific structural targets of the brain. DBS is commonly utilized in the management of a wide spectrum of diseases. Foremost among these are movement disorders, and in particular Parkinson's disease (PD). However, the target of the stimulation for PD can differ depending on the clinical scenario. Typically, the preferred target is the subthalamic nucleus (STN). However, in a small minority of cases, the internal segment of the globus pallidus interna (GPi) may be preferable.[1]

The role of DBS in the management of motor symptoms is well defined, with a wealth of evidence demonstrating the significant and consistent benefits of DBS on this symptomatic domain.[2–4] However, it is becoming increasingly clear that the influence of DBS also extends to the non-motor phenomena observed in movement disorders. Indeed, PD is recognized as a condition characterized by both motor problems and non-motor symptoms, such as autonomic dysfunction, and STN-DBS can impact urinary, cardiovascular, gastrointestinal, and thermoregulatory symptoms as well as sexual activity.[5]

[1]Clinical Ageing Research Centre, Newcastle University, Newcastle Upon Tyne, United Kingdom; [2]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom; [3]Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

*Correspondence to: Dr. Laura A. Best, Clinical Ageing Research Centre, Newcastle University, Campus for Ageing & Vitality, Westgate Road, NE4 5PL, Newcastle upon Tyne, UK; E-mail: laura.best@newcastle.ac.uk
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The effects of STN-DBS on motor and nonmotor symptoms are determined not only by the intensity of the electrical stimulation but also by the location of the stimulating electrode within the STN.[6] Despite such observations, only 1 published study has directly investigated the impact of STN-DBS on autonomic symptoms in PD[5] using the self-administered Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms questionnaire, showing a significant scores reduction one month after DBS ($P = 0.002$).[7]

On the other hand, DBS could be responsible for autonomic side effects in patients with motor disorders, including orthostatic hypotension[8] and syncope.[9] Such unpleasant side effects of DBS have not been investigated systematically and have only described in single case reports.

In this article, we review the published literature to better delineate the positive clinical improvements and the negative occurrence of changes in autonomic function following both STN-DBS and GPi-DBS in PD patients. We anticipate that this overview will enhance understanding of how DBS can modulate the autonomic nervous system and improve the clinical information we provide to our patients as well as their ongoing management post-DBS surgery.

Methods

We conducted a PubMed research of published articles from January 2001 regarding the effects of the DBS on the autonomic system using the following keywords: deep brain stimulation; subthalamic nucleus; globus pallidus interna; autonomic dysfunction; blood pressure; heart rate; sweating; hyperhidrosis; bladder disfunction; micturition; gastrointestinal motility; constipation; sexual disfunction; Parkinson's disease. We have then presented the results with respect to individual domains of autonomic function and the impact DBS can have symptomatically.

Urinary Domain

Urinary symptoms are present in 38% to 71 % of patients with PD, with the most frequently reported symptom being nocturia followed by urgency and frequency.[10] It is possible that the relative degeneration of the caudate nucleus could explain bladder dysfunction,[11] and according to the Braak hypothesis, the threshold for emergence of urinary dysfunction could be the involvement of the neocortex in the disease process.[12] These pathological changes may lead to an earlier perception of bladder sensation, resulting in detrusor overactivity and is likely caused by the modulation of bladder afferents and central sensory processing by the STN.[10]

Depending on the area of the brain that is stimulated, DBS can both induce or inhibit micturition. The basal ganglia, most likely D1-GABAergic direct pathway, and the periaqueductal gray (PAG) area of the brainstem seem to be able to inhibit micturition and improve urinary incontinence.[13] Both substantia nigra pars compacta neuronal firing and the released striatal dopamine seem to activate the dopamine D1- GABAergic direct pathway, which projects to the substantia nigra pars reticulata and to the GPi. The direct pathway does not only inhibit the basal ganglia output nuclei but also may inhibit the micturition reflex via GABAergic collateral to the micturition circuit.[13]

The PAG acts as a relay station for information ascending from the bladder via the spinal cord and signals coming from higher cortical areas.[13] It is proposed that stimulation via the STN-DBS improves the storage capacity of the bladder through the normalization of the basal ganglia and thalamic circuits, which are altered in PD. This results in the appropriate transfer of sensory information regarding bladder sensation from the PAG to the cortex and restoring physiological set points for detrusor contraction and voiding as well as increasing bladder capacity in the storage phase.[14]

Experimental studies further support basal ganglia involvement in bladder contraction. For example, electrical stimulation of the substantia nigra, STN, and globus pallidus has been shown to inhibit the micturition reflex in cats.[15] Using a murine model, Pazo[16] demonstrated that electrical stimulation of the dorsomedial striatum elicited bladder wall contraction and increased excitability of the micturition reflex, whereas stimulation of the ventromedial striatum and globus pallidus inhibited detrusor contractions and increased the micturition reflex.

The modulation of brain areas through STN-DBS essential to autonomic function and control of micturition has also been demonstrated using functional imaging studies. Positron emission tomography (PET) studies consistently support the theory that STN-DBS produces changes in the neural activation of frontal cortical regions, including the supplementary motor area[17] and anterior cingulate gyrus.[18] These structures play a role in urinary function as revealed in other PET and magnetic resonance imaging studies.[18,19] Furthermore, anatomical connectivity and electrophysiological studies suggest that STN-DBS influences the activity of the GPi and the substantia nigra pars reticulata. Both of these structures transfer striatal information to downstream thalamic nuclei, namely, the ventral anterior and ventral lateral nuclei, and from there to the frontal cortex, supplementary motor area, and dorsolateral prefrontal cortex.[20]

Although STN-DBS has been shown to have positive benefits by improving abnormal urodynamic parameters in PD patients with lower urinary tract symptoms,[21] there have been cases in the literature where stimulation has resulted in significant urinary dysfunction. Fritsche and colleagues[22] reported 2 patients who developed acute urinary retention following STN-DBS, most likely attributed to suboptimal positioning of the electrodes. Fortunately, in both cases, reduced detrusor activity was an early and temporary complication that was resolved within the first 3 months postoperatively.[22] Another study by Buhmann and colleagues[23] reported urinary incontinence occurring in the first 6 months postoperatively in 4 of their 82 patients who underwent STN-DBS for PD, all of whom underwent uncomplicated transurethral preoperative catheterization. In each case, signs of urinary incontinence were already present prior to the initiation of high-frequency stimulation of the STN, leading the authors to suggest that this could imply microlesioning effects or the residual effects of anesthesia.[23]

Aviles-Olmos and colleagues[24] have reported a case of a patient with PD and levodopa refractory gait symptoms who developed detrusor overactivity immediately after right pedunculopontine nucleus (PPN)-DBS. In their opinion, the proximity between the caudal pedunculopontine nucleus and brainstem structures implicated in the control of micturition was a possible explanation.

A further study by Mock and colleagues[21] analyzed the lower urinary tract symptoms in PD patients undergoing STN (n = 20) and GPi (n = 13) DBS. They found that urologic quality of life scores improved overall following DBS. However, when analyzed by target, only the STN showed a significant change in quality of life (3.20 ± 1.61 vs. 2.25 ± 1.33; $P = 0.04$).

Larger studies will be needed in future studies to better quantify differences in DBS outcomes between the 2 structural targets (Table 1).

Gastrointestinal Domain

Nausea, gastroparesis, vomiting, dyspepsia, dribbling of saliva, chronic constipation, and dysphagia are reported in up to 80% of patients with PD.[25] Gastrointestinal dysfunction in PD is pathologically complex, likely resulting from extranigral degeneration, such as in the dorsal vagal nucleus or in the intramural intestinal plexus.[26] For example, constipation may result from a different combination of disease affecting the central nervous system (secondary to neural loss and Lewy-type synucleinopathy in the dorsal motor nucleus of the vagal nerve and spinal cord) and the peripheral nervous system (as a result of a rostral–caudal gastrointestinal gradient of Lewy-type synucleinopathy).[27]

Similarly, dysphagia in PD is likely attributed to Lewy-type synucleinopathy pathology affecting the pharyngeal nerves and localized muscle atrophy.[28] However, some patients may also have abnormal oesophageal peristaltic movements, which could be modulated by DBS through the vagal nerve.[29] A study using video fluoroscopy found improvements in some aspects of pharyngeal swallowing following STN-DBS,[30] leading the authors to postulate that STN-DBS could potentially modulate thalamocortical or brainstem targets and overcome the bradykinesia and hypokinesia associated with pharyngeal muscles in PD. However, whether this brings about a clinical benefit remains to be clarified. In a recent manometric study in 16 PD patients following STN-DBS, Derrey and colleagues[31] demonstrated significant improvement in oesophageal body contractions and enhancement of lower oesophageal sphincter opening. On the other hand, Troche and colleagues[32] reviewed 9 studies specifically addressing the effects of DBS on swallowing, but did not find clinically significant effects of DBS on swallowing function, either in improving or worsening of dysphagia.

A case report has detailed the negative effects of STN-DBS on the swallowing function. The authors describe the case of a 74-year-old man with PD post-bilateral STN-DBS implantation who subsequently developed a weak cough, stridor, tachypnoea, and aspiration.[33] His swallowing function was assessed ON stimulation during video-fluoroscopic examination revealing the aspiration of thin liquids. Following a 1-hour washout period in the stimulation OFF state, aspiration was not observed, and the patient reported a subjective 80% improvement of cough and swallowing function.[33]

When directly comparing the effect of DBS on swallow depending on the anatomical target, the aforementioned review by Troche and colleagues suggested that STN-DBS appears to cause more impairment compared to GPi-DBS.[32] This statement

TABLE 1 *Summary of the clinical effects on the urinary system following DBS implantation*

Study	Target	Patient Number	Comparison Group	Investigation Methods	Length of F-U	Clinical Effects
Herzog et al[14]	STN	9	None	PET scans, urodynamic measurements	None	The mean bladder volumes at the desire and the urge to void (points 3 and 4 of the rating scale, respectively) increased significantly
Herzog et al[20]	STN	11	None	PET scans, urodynamic measurements,	None	Significant higher volumes for the first desire to void and urge to void
Mock et al[21]	20 STN 13 GPi	33	None	American Urological Association, Quality of Life score, Overactive Bladder 8 Questionnaire, and Sexual Health Inventory for Men	6 months	After STN-DBS, improvements in Quality of Life score for lower urinary tract symptoms in PD patients with moderate lower urinary tract symptoms
Fritsche et al[22]	STN	2	None	International Prostate Symptom Score	2/3 months	Transient acute urinary retention following DBS
Buhmann et al[23]	STN	82	None	Discharge letters, reports from the outpatient clinics, surgical reports	3 years	Urinary incontinence in 4 patients

DBS, deep brain stimulation; F-U, follow-up; STN, subthalamic nucleus; GPi, globus pallidus interna; PET, positron emission tomography; PD, Parkinson's disease.

is further supported by a multicenter, retrospective study in which only patients who underwent STN-DBS reported postoperative dysphagia.[34] Furthermore, one study investigating jaw velocity following STN-DBS compared to GPi-DBS found that STN-DBS negatively affected voluntary jaw velocity, including the loss of the preoperative levodopa-induced improvement, whereas in the GPi-DBS group there was an observed improvement postoperatively.[35] Although this may have implications for swallow in patients, there have been no directly comparative studies between STN-DBS and GPi-DBS, meaning evidence-based conclusions are yet to be drawn.

In a more general context, a comparative study by Rukmini Mridula and colleagues[36] demonstrated that gastrointestinal symptoms were significantly lower in patients with STN-DBS (67.8%) compared with PD patients on dopaminergic therapy only (94.3%). In particular, the most significant difference concerned the troublesome symptoms of sialorrhea, constipation, nausea, and vomiting,[36] echoing an earlier study demonstrating that bilateral STN-DBS improves salvation, swallow, and constipation.[37] Similarly, Krygowska-Wajs and colleagues[38] found reductions in common gastrointestinal symptoms, including dysphagia (50% to 25%), sialorrhea (35% to 15%), constipation (95% to 75%), and difficulties in defecation (85% to 50%) in patients who underwent STN-DBS. Pietraszko and colleagues[39] also reported significant improvements in parameters including salivation and constipation as well as abdominal pain and rectal burning during or after defecation. Improvements in gastric emptying, which is typically delayed in PD, have also been attributed to STN-DBS. For example, using the ^{13}C-acetate breath test, Arai and colleagues[40] found an improvement following DBS expressed as the peak time for ^{13}C-acetate excretion as a reflection of gastric emptying. This finding is further supported by a multicenter, prospective study by Dafsari and colleagues[41] again showing improved gastric emptying following STN-DBS, albeit determined using patient-directed questionnaires.

Rizzone and colleagues[42] followed 26 PD patients who had undergone STN-DBS surgery for 11 years postoperatively. Of these cases, severe constipation was reported by 4 patients at baseline, with 2 of them demonstrating improvement at follow-up, whereas an additional 5 patients had developed it postoperatively.[42] This could be attributed to the progressive worsening of the disease, but also may a result of the reduction of dopaminergic treatment. For example, Tateno and colleagues[43] observed an improvement in bowel frequency and difficulty defecating in de novo PD patients pre-levodopa and post-levodopa treatment. A further study by Bellini and colleagues[44] demonstrated an inverse trend between eosinophilic density and levodopa dose, suggesting a reduction in bowel inflammation related to levodopa therapy. Further work is required to better delineate the role DBS plays in the modification of constipation symptoms.

Another significant problem for patients undergoing STN-DBS is weight gain. The STN is commonly associated with both reward and inhibitory control pathways.[45] Indeed, food craving and binge eating have been frequently reported following STN-DBS surgery,[46,47] and patients with other pathology affecting the STN, for example, stroke or tumur, can also experience hyperphagia and increased appetite.[48] Alternatively, the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of energy metabolism or the homeostatic pathway of food intake.[49]

One study reported that patients with at least 1 contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally, suggesting involvement of the limbic system.[49] Aiello and colleagues[50] studied food reward sensitivity (liking, wanting, and preference) and a food "go/no-go" task to examine the impulsivity of patients undergoing STN-DBS before, a few days after, and months following the operation. A few days after surgery, patients demonstrated increased impulsivity in the food go/no-go task, showing a preference for high calorie foods. As one would expect, this coincided with significant weight gain postoperatively. Months after STN stimulation, the impulsivity improved, but no differences were observed in reward sensitivity.[50] Such results are consistent with animal studies looking at STN stimulation or lesioning, which again demonstrate an increase motivation toward food following the procedure and a preference for high calorie foods.[51] The Aiello study further highlighted that weight gain postoperatively negatively correlated with levodopa therapy reduction, that is, the greater the medication reduction the more weight gain, and this also corresponded to disease duration.[50]

Concerning GPi-DBS, Sauleau and colleagues[52] performed a PET study of PD patients following surgery. As with studies focusing on STN-DBS, they found that body mass index increased significantly following surgery. Examining brain activity prospectively, they highlighted a significant inverse relationship between weight gain and brain metabolism in the motor areas of the brain, such as the premotor and somatosensory association cortices. However, there was no correlation between brain metabolism in limbic and associative areas.[52]

Several other theories as to why weight gain occurs following DBS surgery have also been put forward, including changes in energy metabolism, as a result of motor improvement or secondary to improvements of dysphagia. In another study carried out by Sauleau and colleagues, they suggested that the diminished energy expenditure following motor improvement and the reduction of dyskinesias could contribute to weight gain in these patients. They observed that changes in body mass index correlated with reduced dyskinesia in PD patients undergoing pallidal DBS.[53] However, in the following PET study, where they investigated 19 patients (9 men, mean age at surgery 61 $\pm$ 8 years) with idiopathic PD assigned to bilateral GPi-DBS, they observed only a trend toward a correlation between the reduction in dyskinesias and weight gain.[52] Another study found a correlation between weight gain and improvements in UPDRS part III scores and dyskinesias; however, the surgical procedure (9 unilateral pallidotomy, 9 bilateral pallidal DBS, 9 bilateral STN-DBS) was too heterogeneous to lead to any firm conclusions.[54]

This further emphasizes the complexity regarding the mechanisms causing weight gain in patients postoperatively, and it is likely that the differences in weight changes observed after both STN and GPi stimulation are multifactorial (Table 2).

TABLE 2 *Summary of the clinical effects on the gastrointestinal system following DBS implantation*

Study	Target	Patient Number	Comparison Group	Investigation Methods	Length of F-U	Clinical Effects
Ciucci et al[30]	STN	14	None	Radiographic swallow studies	None	Improvement in the bradykinesia and hypokinesia of the pharyngeal muscles
Derrey et al[31]	STN	16	None	Oesophageal high resolution manometry	6 months	Improvement in oesophageal body contractions and enhancement of lower oesophageal sphincter opening
Fagbami and Donato[33]	STN	1	None	Direct laryngoscopy, clinical and fluoroscopic swallowing examination	None	Case report of a patient developing dysphagia and aspiration associated with stimulation adjustment
Rukmini Mridula et al [36]	STN	56	53 age and duration of illness matched PD patients on dopaminergic therapy	NMS Questionnaire	None	Improvement in sialorrhea, constipation, nausea and vomiting, dysphagia, abdominal pain
Zibetti et al[37]	STN	36	None	UPDRS, patient clinical charts	24 months	
Krygowska-Wajs et al[38]	STN	20	None	Structured gastrointestinal questionnaire, electrogastrography	3 months	
Pietraszko et al[39]	STN	19	None	Structured gastrointestinal questionnaire	3 months	
Arai et al[40]	STN	16	None	^{13}C-acetate breath test	3 months	Improvement of gastric emptying
Dafsari et al[41]	STN	60	None	Non-Motor Symptoms Scale, NMS Questionnaire	6 months	
Rizzone et al[42]	STN	26	None	Clinical assessment	10–13 years	4 patients reported severe constipation preoperatively, improvement in constipation in 2 of them after DBS. 5 patients developed severe constipation postoperatively during the follow-up

DBS, deep brain stimulation; F-U, follow-up; STN, subthalamic nucleus; PD, Parkinson's disease; NMS, non-motor symptoms; UPDRS, Unified Parkinson's Disease Rating Scale.

Cardiovascular and Pulmonary Domain

Cardiac autonomic disturbances are commonly reported in PD. For example, orthostatic hypotension is frequently described, and treatment with levodopa, as well as other antiparkinsonian medications, can often worsen these symptoms.[55] In a study by Ludwig and colleagues,[56] the authors evaluated the effect of STN-DBS compared with levodopa medication, analyzing cardiovascular parameters including blood pressure and heart rate variability. They found that although levodopa worsened orthostatic hypotension, STN-DBS only caused cutaneous vasoconstriction, with no other cardiovascular disturbances reported. The authors surmised that the effect of levodopa may have been secondary to a reduced sympathetic outflow caused by D2 receptor stimulation, with STN-DBS comparatively only having a minor influence on the cardiovascular system.[56]

On the other hand, Dafsari and colleagues,[41] in a multicenter prospective study, demonstrated a trend toward an overall improvement in cardiovascular outcomes 6 months following STN-DBS surgery. Similarly, Rukmini Mridula and colleagues[36] found a significant reduction in cardiovascular symptoms reported by PD patients at a time point greater than 1-year postbilateral STN-DBS, with only 18 patients (32.14%) reporting cardiovascular problems compared with 33 patients (62.2%) reporting similar issues on dopaminergic therapy alone. Furthermore, in this study, symptomatic orthostatic hypotension, evaluated by the reporting of light-headedness, was significantly lower in the STN-DBS group.[36] However, it should be noted that in the treatment-only cohort, the levodopa equivalent dose was significantly higher compared with the DBS cohort, which may also offer an explanation for the increased incidence of cardiovascular symptoms. The difference in mean disease duration was not significant.

In contrast, Holmberg and colleagues[57] found that, after 1 year, heart rate variability and blood pressure during tilt was reduced compared with baseline measurements to a similar extent in patients who underwent STN-DBS (n = 11) and those who received optimized medical treatment (n = 8). This was observed despite medication reduction in the patients who underwent DBS.[57] Furthermore, the number of individual cases associated with abnormal autonomic tests after 1 year increased only in the STN-DBS group, leading the authors to conclude that STN-DBS does not appear to confer a cardioprotective effect. Similarly, Trachani and colleagues[58] reported no considerable impact on blood pressure or heart variability following STN-DBS at 6 months postsurgery, and other publications have also reported conflicting findings on the cardiovascular effects of STN-DBS.[59]

The stimulation of specific subregions of the STN could produce different changes in the heart rate of PD patients treated with STN-DBS. Benedetti and colleagues[60] have reported that the stimulation of the dorsal most region, including the zona incerta and the dorsal pole of the STN, almost always led to an increase in heart rate, even when the patients were not aware of being stimulated (hidden vs. open stimulation). Conversely, the stimulation of the ventral most region, which includes the ventral pole of the STN and the substantia nigra pars reticulata, caused variable changes in heart rate, with significant increases only when the patients were aware of being stimulated (open stimulation).[60] The authors suggest that the dorsal STN and/or the zona incerta could be directly involved in autonomic control, whereas the ventral STN and/or the substantia nigra reticulata could be involved in associative/limbic-related autonomic activity.[60]

Therefore, the real impact of STN-DBS on the cardiovascular system remains undetermined, and further randomized, long-term studies are required to evaluate any positive outcomes on the cardiovascular system irrespective of disease progression and medication effects.

There have been reported cases of significant cardiovascular adverse effects following stimulation. Sanchez-Ferro and colleagues[61] reported cases of hypertensive crisis after stimulation as a consequence the electrode being placed medially in the subthalamus.[61] This likely resulted in unwanted activation of the posterior hypothalamus near the STN, causing stimulation-induced autonomic effects.[62] Williams and colleagues[8] described a case of a PD patient who developed orthostatic hypotension after STN stimulation. Holter monitoring demonstrated first-degree heart block with pauses of up to 4 seconds, requiring the patient to be fitted with a dual-chamber permanent pacemaker. The pacemaker relieved the electrocardiographic abnormalities, but not the symptoms of syncope. Similarly, Aygun and colleagues[9] described a female patient who developed syncopal episodes following STN-DBS surgery. The right electrode was placed centrally within the STN and the left electrode within the anterior part of the STN.[9] During surgery, when the left STN was stimulated at 5 milliampere, the patient developed presyncopal symptoms. However, when the stimulation was stopped her symptoms improved. During the early period after DBS surgery, when the right STN was stimulated at 1.3 millivolts, she developed the presyncopal symptoms and then syncope.[9] Furthermore, Kenney and colleagues[63] reviewed 319 DBS cases, including 182 PD patients, and reported 8 (2.5%) who developed vasovagal response and 4 (1.2%) who developed syncope following DBS. In another study of 14 PD patients with STN-DBS in situ, 3 patients developed orthostatic hypotension when stimulation was ON, 2 when stimulation was OFF, and 3 patients developed it under both conditions.[56] Such reports indicate the importance of screening patients for autonomic symptoms following surgery, even if they have not been symptomatic prior to stimulation, to avoid untoward side effects and prevent harm.

Thornton and colleagues[64] investigated heart rate and mean arterial blood pressure in patients with movement disorders (n = 13 PD, n = 1 myoclonic dystonia, n = 1 spasmodic torticollis) undergoing stereotaxic neurosurgery for either the placement of electrical stimulating electrodes or electrolytic lesioning of the STN, GPi, ventralis intermedius thalamus, or ventralis oralis posterior thalamus. In this study, patients with the GPi electrical stimulation (n = 6) appeared to have no modifications of cardiovascular function.[64]

There is little in the literature regarding the effect of DBS on respiratory function.

Kataoka and colleagues[65] have reported a case of a 76-year-old PD patient treated STN-DBS who developed severe dyspnea following some readjustment to his DBS settings. A fiber-optic examination of the larynx showed an abnormal, possibly dystonic, positioning of the epiglottis that covered the top of the trachea causing dyspnea. Interestingly, the abnormal positioning of the epiglottis was aggravated by increasing the voltage of STN stimulation and relieved by decreasing the voltage.[65]

Hyam and colleagues[66] investigated patients with DBS targeting the STN, PAG, and sensory thalamus. They found changes were only associated with STN and PAG-DBS, with an increase in the peak expiratory flow rate, but no change in forced expiratory volume in one second[66] (Table 3).

Thermoregulatory Domain

Animal studies regarding the locations of autonomic tracts have shown that efferent signals from the preoptic hypothalamus travel via the tegmentum of the midbrain, pons, and the medullary raphe regions to the intermediolateral cell column of the spinal cord.[67] Nevertheless, there is limited evidence about the precise location and connections of thermoregulatory centers in humans.[68]

A search of the literature provides contradictory results regarding the effect of STN-DBS on the thermoregulatory function. Dafsari and colleagues found significant improvement in hyperhidrosis at a 6-month follow-up,[41] in contrast to other studies that did not identify any improvement.[69] In a study by Trachani

TABLE 3 *Summary of the clinical effects on the cardiovascular system following DBS implantation*

Study	Target	Patient Number	Comparison Group	Investigation Methods	Length of F-U	Clinical Effects
Williams et al[8]	STN	1	None	Holter monitoring, formal tilt table-assessment.	None	Case report of orthostatic hypotension and first-degree heart block following stimulation
Aygun et al[9]	STN	1	None	Patient symptoms.	None	Case report of syncopal episodes associated with stimulation
Rukmini Mridula et al[36]	STN	56	53 age and duration of illness matched PD patients on dopaminergic therapy	NMS Questionnaire	None	Lower frequency of orthostatic hypotension compared with levodopa treatment
Dafsari et al[41]	STN	60		Non-Motor Symptoms Scale, NMS Questionnaire	6 months	
Ludwig et al[56]	STN	14	15 non stimulated PD patients	Noninvasive laser Doppler flowmetry/ computer-assisted equipment	None	Cutaneous vasoconstriction reported. Development of orthostatic hypotension in 8 of 14 patients in the study
Holmberg et al[57]	STN	11	8 PD patients on dopaminergic therapy 10 matched healthy subjects	Noninvasive finger blood pressure, autonomic sphygmomanometry, tilt test, electrocardiogram.	1 year	Reduction of heart rate and blood pressure after 1 year
Sanchez-Ferro et al[61]	STN		None		None	Hypertensive crisis observed with medial lead placement (unpublished data, authors experience)
Kenney et al[63]	STN	182	None	Retrospectively assessed	None	Vasovagal response (2.5% of patients) and syncope (1.2% of patients)
Kataoka et al[65]	STN	1	None	Fiber-optic examination of the larinx	None	Case report of a patient developing a fixed, rigid epiglottis associated with stimulation

DBS, deep brain stimulation; F-U, follow-up; STN, subthalamic nucleus; PD, Parkinson's disease; NMS, non-motor symptoms.

and colleagues,[70] no objective reduction in hyperhidrosis was demonstrated through the recording of sympathetic skin response in 19 postoperative patients, although subjective improvement was reported via a semistructured questionnaire. A further study reported STN-DBS improved sweating during motor OFF periods in PD patients and markedly reduced fluctuations in thermoregulation.[71] In addition, Halim and colleagues[72] found that the beneficial effects of STN-DBS on sweating in 3 patients with early-onset of PD was quite dramatic, and in 1 of them alleviation sweating was accomplished even with unilateral (left) STN-DBS. However, this again was assessed subjectively using a self-directed questionnaire addressing non-motor symptoms.[72]

In contrast with the aforementioned studies, Ramirez-Zamora and colleagues[68] presented data on 2 patients who developed

TABLE 4 *Summary of the clinical effects on the thermoregulatory system following DBS implantation*

Study	Target	Patient Number	Comparison Group	Investigation Methods	Length of F-U	Clinical Effects
Dafsari et al[41]	STN	60	None	Non-Motor Symptoms Scale, NMS Questionnaire	6 months	Improvement in hyperhidrosis at 6 months
Ramirez-Zamora et al[68]	STN	2	None	Clinical assessment	1 year	Two patients with reproducible hyperhidrosis when high frequency applied
Trachani et al[70]	STN	19	19 matched for sex and age healthy controls	Semistructural questionnaire and recording of sympathetic skin response from both palms and 1 sole	6 months	Subjective improvement reported
Halim et al[72]	STN	11	None	Autonomic function questionnaire validated in previous study	None	Dramatic improvement in symptoms for 3 patients (n = 11) even with unilateral stimulation

DBS, deep brain stimulation; F-U, follow-up; STN, subthalamic nucleus; NMS, non-motor symptoms.

TABLE 5 *Summary of the clinical effects on sexual functioning following DBS implantation*

Study	Target	Patient Number	Comparison Group	Investigation Methods	Length of F-U	Clinical Effects
Kurcova et al[5]	STN	24	None	International Index of Erectile Function and Female Sexual Function	5 months	No significant effects
Rukmini Mridula et al[36]	STN	56	53 age and duration of illness matched PD patients on dopaminergic therapy	NMS Questionnaire	None	Higher frequency of sexual impairment compared to patients on medication only
Castelli et al[73]	STN	31	None	Reduced form of the Gollombok Rust Inventory of Sexual Satisfaction	1 year	Improvement of sexual functioning in male patients
Teive et al[76]	STN	7 PD patients (only 2 under DBS)	None	Hypersexual disorder and paraphylias were diagnosed according to Kafka and *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria, respectively	5 year	Hypersexual disorder observed following DBS, improved during the F-U

DBS, deep brain stimulation; F-U, follow-up; STN, subthalamic nucleus; PD, Parkinson's disease; NMS, non-motor symptoms.

reproducible hyperhidrosis with high-frequency STN-DBS. In the authors' opinion, the stimulation of the medial zona incerta, as well as the medial and anterior STN, caused hyperhidrosis. Something that has been described in primate and rat models. The hypothesis is that central autonomic fibers originating in the lateral hypothalamic area project laterally to the ventral/medial zona incerta and then to brainstem nuclei following a medial and posterior trajectory in relationship to STN[68] (Table 4).

Sexual Domain

Castelli and colleagues[73] investigated the impact of STN-DBS on sexual function through a self-administered questionnaire. Male patients with PD 1-year after bilateral STN-DBS surgery presented a small but significant improvement in sexual functioning, especially those younger than 60 years of age. No differences in sexual functioning were found presurgery or postsurgery in the female cohort.[73] The change in activity of medial preoptic anterior hypothalamic nuclei and DBS stimulation of projections to the nucleus accumbens is thought to influence sexual activity.[74]

There are, however, conflicting results. For example, Rukmini Mridula and colleagues[36] found a significantly higher frequency of sexual impairment in STN-DBS patients compared with PD controls, that is, those on medication only. This is in contrast to a recent study by Kurcova and colleagues,[5] which used the International Index of Erectile Function and Female Sexual Function[75] to evaluate patients at baseline, 1 month, and 4 months following surgery. They identified no significant difference or trend between the mean values of International Index of Erectile Function at baseline, 1 month, and 4 months postoperatively.[5] The results regarding the female cohort were not deemed relevant because of the low sample size.

Additional negative consequences of STN-DBS have also been reported. Most notably increased sexual arousal and hypersexual disorder (HSD). In 1 prospective study, 2 PD patients (both male) were identified to have HSD following bilateral STN-DBS.[76] However, it is well recognized that HSD is also observed in PD patients who have not undergone DBS surgery as a consequence of dopaminergic agonist medication and levodopa abuse. In this particular study, the adjustment of DBS parameters resulted in an improvement in HSD symptoms in at least 1 of the patients; however, it is not clear if this also coincided with medication reduction[76] (Table 5).

Conclusions

DBS is an effective method for the treatment of motor symptoms in patients with PD. However, it could also be used in the future to intervene specifically on other aspects of the disease, such as autonomic dysfunction and non-motor symptoms.

Generally, these studies demonstrate beneficial outcomes for patients. In particular, regarding STN-DBS on the urinary and gastrointestinal domains in patients with PD, with effects at the level of the cardiovascular, pulmonary, thermo-regulatory, and sexual domains more controversial because of the limited evidence and conflicting results.

However, it should be acknowledged that several factors other than a direct DBS effect could be responsible for the changes in autonomic symptoms post-DBS surgery. In fact, many of the published studies did not include matched controls, medication changes post-DBS and disease progression were not taken in account, and in addition, the changes in autonomic symptoms were often reported as subjective. Further studies will be needed to clarify the relationship between DBS and the autonomic system, taking into consideration variables such as disease progression, medication effects, and electrode placement. Through improved understanding of stimulation effects, it may be possible to calibrate the target for each patient as accurately as possible providing more personalized care and improved symptom management.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the first draft, B. Review and Critique.

G.B.: 1A, 1B, 2A
L.A.B.: 1A, 1B, 2B
U.B.: 2B
R.M.: 2B
N.P.: 1A, 1B, 2B

Disclosures

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The authors confirm that the patient consent was not required for this work. The authors confirm that the approval of an institutional review board was not required for this work.

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